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(54) Title: POLYMER PARTICLES MADE OF POLYVINYL ALCOHOL AND COMPRISING A CONTRAST AGENT FOR CHEMOEMBOLIZATION

(57) Abstract

The invention relates to an embolizing composition comprising a particulate biotolerable organic polymer having immobilized therein or thereon a contrast enchancing material.

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POLYMER PARTICLES MADE OF POLYVINYL ALCOHOL AND COMPRISING A CONTRAST AGENT FOR CHEMOEMBOLIZATION

FIELD OF THE INVENTION

The present invention relates to biotolerable polymer particles, especially polvinylalcohol (PVA) particles, their use in chemoembolization, for example in the treatment of tumors, and their preparation.

BACKGROUND OF THE INVENTION

Chemoembolization is a technique in which a particulate agent is administered into the vasculature which, due to particle size or particle aggregation, causes capillary blockage (embolus formation) and hence a reduction or cessation of blood flow to a target site in the body, usually a tumor. This in turn results in necrosis of the targeted tissue. The technique is particularly attractive where surgical removal of tumors is excluded, for example due to poor health of the patient, and the technique has been used for example to treat hepatocellular carcinomas, melanomas, head and neck cancers and fibroid tumors of the uterus.

The embolizing agents used in this technique either contain solid particles, such as PVA or gelfoam particles, or oil droplets (e.g. as in ethiodol (trade name Lipiodol)).

The oil droplets in ethiodol are of an iodinated organic compound. Accordingly the emboli may be located using X-ray CT imaging procedures. The use of oil droplet embolizing agents however has the drawback that the droplets can break down into smaller droplets which can pass through the target tissue and cause undesired and particularly harmful emboli in tissues distant from the target tissue, e.g. in the lungs.

The solid embolizing agents, such as gelfoam and PVA particles, require coadministration of a contrast agent (e.g. the water-soluble iodinated X-ray contrast

agent iohexol (trade name Omnipaque) or the water-soluble paramagnetic magnetic resonance imaging agent gadodiamide (trade name Omniscan)) in order that the locations of the emboli may be detected using conventional imaging procedures. This is achieved by following the blood vessel of interest, highlighted by the contrast agent, until contrast enhancement is lost. At this point it is inferred that the embolus is located where the contrast agent is blocked from further migration down the vessel of interest. This technique however can lead to inaccurate diagnoses and diminished prognoses for the patient if the embolus is not in fact located at the point where contrast enhancement stops being discernible in the X-ray or mr image.

An alternative proposal for more accurate determination of embolus location has been to soak PVA particles, which are porous, in a contrast agent before the initial placement of the embolizing agent. However this too has the drawback that the contrast agent diffuses out of the particles at the embolus site and thus on follow-up examination, e.g. at one week or later following embolus formation, the embolizing agent is no longer visualisable making it necessary at that stage to administer a contrast agent and infer the location of the emboli from the cessation of contrast enhancement in the blood vessel of interest as described above.

There is thus a continuing need for embolizing agents which combine the particle size integrity of the solid agents with the continuous contrast enhancing efficacy of ethiodol.

SUMMARY OF THE INVENTION

We have now found that contrast effective materials may be effectively immobilized within biotolerable polymer particles to produce contrast enhancing embolizing agents.

Thus viewed from one aspect the invention provides

an embolizing composition comprising a particulate biotolerable organic polymer having immobilized therein (e.g. in pores thereof or within microballoons thereof) or on the surface thereof a contrast enhancing material.

By immobilized it is meant that the polymer particles retain a contrast enhancing effect *in vivo* for a prolonged period of at least 7 days, preferably at least 14 days and particularly preferably until the particles biodegrade. Indeed where the particles are non-degradable, it is preferred that the contrast enhancing effect be essentially permanent. Adequate retention of contrast enhancing properties may conveniently be tested *in vitro* by disposing the particles in a blood substitute such as Fluosol®, animal plasma, human plasma or saline. Particles which retain at least 50% (preferably at least 80%) contrast efficacy for the periods specified above may be considered to contain an immobilized contrast enhancing material.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 of the accompanying drawings is a CT (ie. X-ray) scan of polyvinyl alcohol particles (sponges) containing Fe(III) or Fe(III) and an iodinated contrast agent and scanned in air at 140 kV/150 mA.

DETAILED DESCRIPTION

The biotolerable organic polymer in the agent of the invention may be any organic polymer capable of forming porous particles or microballoons and tolerated by the human or animal body. The polymer may be non-biodegradable or biodegradable, e.g. polymers which break down *in vivo* over a period of less than one year. Suitable polymers include double ester polymers, polyacrylate, polyvinylacetate, polyacrylonitrile, urethane/carbonate polymers, styrene/maleic acid polymers, polymethacrylate, polypeptides, gelatin, celluloses (e.g. cellulose acetate or nitrocellulose),

ethyl vinyl alcohol polymers or more preferably polyvinyl alcohol, polylactide-co-glycolide, Beb Lansen type polymers, etc.

The preparation of porous polymer particles and polymer microballoons is a well-known procedure and is described broadly in the literature, see for example Derdeyn et al. AJNR 16: 1335-1343 (1995), Berenstein et al. Radiology 145: 846 (1982), Kim et al. in "Polymeric materials: Science and Engineering", Proc. ACS Division of Polymeric Materials: Science and Engineering, Vol. 63, 1990, page 64, and the documents referred to therein.

The polymer particles in the agents of the invention preferably have mean particle sizes in the range 10 to 2000 μm, especially 50 to 1000 μm, more especially 100 to 700 μm, particularly 150 to 600 μm. Appropriate particle sizes may be produced by stepwise particle growth, or controlled precipitation or by milling and/or size fractionation. Particularly advantageously the particles are substantially monodisperse, e.g. with 90% by weight or more of the particles having a size within 10% of the mean particle size.

The contrast enhancing material in the particles may be any material capable of enhancing contrast in a desired imaging modality (e.g. magnetic resonance, X-ray (e.g. CT), ultrasound, magnetotomography, electrical impedance imaging, light imaging (e.g. confocal microscopy and fluorescence imaging) and nuclear imaging (e.g. scintigraphy, SPECT and PET)) and capable of being substantially immobilized within the particles.

Immobilization may for example be by chemical or physicochemical interaction between the contrast enhancing material and the polymer matrix (e.g. covalent or ionic bonding or adsorption) or by physical entrapment, for example with the contrast enhancing agent being trapped within pores or voids in the polymer or being held within a non-porous polymer matrix. Where

the polymer is porous, contrast agent may be loaded into the polymer particles which may be surface modified to prevent or reduce diffusion of contrast agent out of the pores, e.g. by coating or pore mouth engineering or cross-linking the loaded particles. Likewise contrast agent may be formed within or deposited within pores of a porous polymer, e.g. by precipitation or by "ship-in-a-bottle" construction of molecules too large to diffuse out of the pores from starting materials small enough to diffuse in. Such particle loading techniques have been extensively described in connection with zeolite particles, e.g. for use as mr imaging contrast agents (cf. US-A-5122363 and US-A-5429814).

Particularly preferred examples of contrast enhancing materials include paramagnetic materials (e.g. persistent free radicals or more preferably compounds, salts and complexes of paramagnetic metal species, for example transition metal or lanthanide ions), heavy atom (ie. atomic number of 37 or more) compounds, salts or complexes (e.g. heavy metal compounds, iodinated compounds, etc.), radionuclide containing compounds, salts or complexes (e.g. salts, compounds or complexes of radioactive metal isotopes or radioiodinated organic compounds), superparamagnetic particles (e.g. metal oxide or mixed oxide particles, particularly iron oxides), gases, preferably lipophilic gases, or gas mixtures (ie. materials which are gaseous at 37°C, e.g. fluorocarbons, for example perfluorobutane and perfluoropentane).

Preferred paramagnetic metals include Gd(III), Dy(III), Fe(II), Fe(III), Mn(III) and Ho(III), and paramagnetic Ni, Co and Eu species.

Preferred heavy metals include Pb, Ba, Ag, Au, W, Cu, Bi and lanthanides such as Gd, etc.

Preferred radionuclides include ^{52}Mn, ^{54}Mn, ^{90}Y, ^{201}Tl, ^{125}I, ^{123}I, ^{32}P and ^{111}In. Generally however radionuclides are not preferred as contrast agents for the particles

of the invention unless used in conjunction with another contrast agent, e.g. an X-ray or mr agent.

Preferred gases include perfluorocarbons such as perfluoropentane, perfluorobutane, and sulphur hexafluoride and other fluorinated agents such as are described in WO96/29783.

Particularly preferably however the contrast enhancing material is a water-soluble iodinated organic compound (preferably a non-ionic agent), a precipitated water-soluble salt of a soluble iodinated organic compound, a water-insoluble compound, salt or complex of a paramagnetic metal, in particular Fe, Mn or Gd, especially Fe or Mn, a superparamagnetic metal oxide particle, a water-insoluble compound, salt or complex of a heavy metal, a lipophilic gas or gas mixture, an entrapped gas or gas mixture, or a water-insoluble compound, salt or complex of a metal radionuclide.

Thus viewed from a further aspect the invention provides an embolizing agent comprising polyvinyl alcohol particles containing an immobilized contrast enhancing material selected from water-insoluble compounds, salts and complexes of paramagnetic metals, in particular Fe, Mn or Gd, especially Fe or Mn, superparamagnetic metal oxide particles, water-insoluble compounds, salts and complexes of heavy metals, lipophilic gases or gas mixtures, entrapped gases or gas mixtures, water-soluble or water-insoluble iodinated organic compounds and water-insoluble compounds, salts and complexes of metal radionuclides.

The contrast enhancing material should be present in the polymer particles in a concentration sufficient to cause an embolus produced by the particles to be visualizable using the selected imaging modality. Accordingly the concentration required will depend upon the selected modality, the chemical and physical form of the contrast enhancing material and the size of the embolus producing particle or particle aggregate. In

general however for particles having a mean particle size in the range 150 to 250 μm, the contrast agent concentration or specific activity should be: for super-paramagnetic particles - at least one superparamagnetic crystal per polymer particle; for radionuclides - at least 0.10 μCi/mg polymer, preferably 1-10μ Ci/mg; for paramagnetic materials - at least 0.02 mmol/mg polymer; for iodinated compounds - at least 0.02 μmol I/mg polymer; for heavy metal compounds - at least 0.02 μmol/mg polymer, preferably at least 0.2 μmol/mg; and for gases - at least 0.01 μmol/mg polymer.

The contrast enhancing material can be loaded into the polymer particles in a variety of ways, e.g. precipitation of a water insoluble material within the pores of porous polymer particles using a gaseous or dissolved precursor; immersion of porous polymer particles in contrast agent solution followed by cross-linking of the polymer, e.g. with formaldehyde; immersion of polymer particles in contrast agent solution followed by treatment to promote bond creation, e.g. sonication or high speed centrifugation; immersion of porous polymer particles in a liquified lipophilic gas or gas mixture; encapsulation of a physiologically tolerable gas or gas mixture; or reaction of the surfaces of porous polymer particles with a reagent serving to couple to the surface a contrast enhancing material, for example via covalent or ionic bonds. Such processes, especially the encapsulation and reaction processes may optionally be carried out under irradiation with light (e.g. UV light) or ionizing radiation.

Viewed from a further aspect therefore the invention provides a process for the production of an embolizing agent according to the invention, said process comprising treating a porous particulate biotolerable organic polymer according to one or more of the following steps: precipitation of a water insoluble material within the pores of the polymer particle from a gaseous or dissolved precursor; immersion of porous polymer particles in contrast agent solution followed by cross-linking of the polymer, e.g. with formaldehyde;

immersion of polymer particles in contrast agent solution followed by treatment to promote bond creation; immersion in a liquified lipophilic gas or gas mixture; or, particularly preferably, reaction of the polymer surface with a reagent serving to couple to the surface a contrast enhancing material, for example via covalent or ionic bonds; or encapsulation of a physiologically tolerable gas or gas mixture within a biotolerable organic polymer.

Thus, taking PVA as an exemplary polymer, porous PVA particles may be treated with a solution of a metal ion of interest, e.g. iron(III) chloride or gadolinium(III) chloride or any other metal ion that can provide contrast in an imaging modality such as mr, X-ray, and nuclear imaging (e.g. dysprosium, europium, lead, tungsten, silver, etc.). Since PVA is a cation exchange resin it will tend to concentrate the metal ions on the polymer surfaces, especially within the pores. The PVA may then be rinsed to remove excess metal ion solution leaving particles which are charged with the metal ion of interest. The metal ion loaded particles may then be exposed to a solution of an anion which forms a water insoluble salt (ie. insoluble at physiological pH) with the metal of interest within the PVA particle. Suitable anions include for example ions which add to X-ray opacity, e.g. iodide and ions of ionic X-ray contrast agents (such as diatrizoate (Hypaque), metrizoate (Amipaque), ioxaglate (Hexabrix), and iodipamide (Cholografin)). Alternatively ions which do not add to X-ray opacity may be used. Thus for example where the cation is a lanthanide, such as gadolinium, oxalate ions may be used to form a precipitate in the PVA particles.

While X-ray opacity can be achieved with heavy metal ions alone, the use of iodinated anions allows contrast to be enhanced still further using known safe anions.

The resulting precipitate loaded particles can be rinsed and dried and stored as dry powders for reconstitution before use. Alternatively they may be retained in a solution of an iodinated contrast agent and administered in this form. This allows maximum CT (X-ray) enhancement during placement of the emboli as contrast arises both from the particles and the surrounding solution. After placement however, contrast derives solely from the particles themselves. For these purposes, the solution preferably contains iodine at a concentration of 10 to 100 mgI/mL, especially preferably 20 to 50 mgI/mL.

As an alternative to treatment with precipitation causing anions, the metal ion loaded particles may be exposed to pH conditions, e.g. elevated pH, that cause the metal ions to form water-insoluble metal oxides, hydroxides or hydrous oxides. Thus for example iron(III) treated particles may be treated to produce particles containing paramagnetic iron oxides or iron(III) and iron(II) treated particles may be base-treated (optimally followed by a heat treatment) to produce particles containing deposited superparamagnetic particles, e.g. of magnetite or lepidicrocite. Such particles could be used to enhance contrast in magnetotomography, mr imaging and CT imaging. Likewise gadolinium(III) ions can be caused to precipitate insoluble, mr contrast effective, gadolinium hydrous oxide at pH levels above 3. Upon drying this hydrous oxide is converted to gadolinium oxide, which is also mr contrast effective. Many other contrast effective metals can likewise be caused to produce insoluble precipitates under the action of a pH change.

The PVA particles may alternatively be treated with a soluble iodide or iodine, e.g. in solution, and subsequently with a solution of a salt of a metal which produces an insoluble iodide, e.g. a silver nitrate solution. The precipitated silver iodide will impart CT

opacity to the particles. Likewise molecular iodine within the PVA particles may be reacted with a solution of a metal compound in which the metal ion is capable of oxidation to a higher oxidation state in which it forms an insoluble iodide salt. Such a reaction would have the advantage of being self limiting as the deposited iodide precipitate would restrict access of the metal reagent into the particles.

An alternative particle loading mechanism is to use reactive precipitation to load the particles with insoluble contrast effective compounds, e.g. metal salts. Thus for example the particles may be loaded with hydrogen sulphide, rinsed and then contacted with a solution of a soluble metal salt the metal whereof is reactive with sulphide to produce an insoluble metal sulphide. Alternatively a metal ion loaded PVA particulate could be flushed with hydrogen sulphide gas or contacted with a solution through which hydrogen sulphide gas is bubbled in order to produce the insoluble metal sulphide precipitate within the particles.

Where the polymer structure has voids interconnected by relatively narrow passages (e.g. as in a zeolite), contrast effective materials too large to penetrate the passages may be created within the voids by successive treatment with reagents which individually are small enough to pass through the passages, e.g. metal ions and linear chelants which, when metallated, adapt a more bulky configuration.

A still further means of loading the particles with contrast effective materials involves reducing metal ions within the particles to produce colloidal metal particles (sols) within the PVA structure. Thus for example PVA particles may be loaded with a reducing agent and then rinsed with oxygen-free water. The particles may then be contacted with a degassed solution of the metal ions (e.g. gold, silver etc.) whereupon

reduction of the metal ions to produce the colloidal metal particles within the PVA particles will occur.

Ultrasound active (ie. echogenic) PVA particles may be produced by impregnating PVA particles with a lipophilic material which is gaseous at body temperature, impregnation preferably being effected after a heat treatment of the particles. Particularly preferably, the gas forming material is liquid when the impregnation is effected, with excess fluid subsequently being drained off. Alternatively, PVA may be used as a stabilizer for an oil-in-water emulsion of a liquid fluorocarbon with a low vapour pressure or any other water-immiscible, physiologically tolerable organic liquid, preferably having a boiling point below 37°C. Once prepared, the emulsion may be freeze-dried to yield hollow PVA particles which can if required be further modified by repeated freeze-drying cycles. Alternatively the PVA encapsulated fluorocarbon or other low boiling material may itself function as an echogenic embolizing agent, especially where the entrapped material forms a gas at 37°C.

Contrast agents that can be loaded into PVA particles include agents which comprise groups that can be linked or crosslinked to PVA groups; agents that can form interpenetrating networks with PVA; agents that can adhere to PVA, and agents that can react with oxidized PVA.

Functional groups on contrast agents that are useful in crosslinking to PVA include hydroxyl groups, especially primary hydroxyl groups ($-CH_2-OH$); amine groups, primary amine groups ($-NH_2$); thiol groups (-SH); active methylene groups such as acetylacetate groups [$-C(=O)-CH_2-C(C=O)-CH_3$] as well as other active methylene groups such as $-C(=O)-CHR'-C(C=O)-$ and $-C(=O)CH_3$ groups where R' is methyl, C_2 to C_{20} alkyl, phenyl, substituted phenyl, alkyl carbonyl, etc.; alpha-beta unsaturated Michael receptor groups such as vinyl

carbonyl groups and vinyl sulfonyl groups; ester groups; carboxylic acid groups; carbonyl groups such as ketones, aldehydes, and ester and lactone groups as well as hydrates of such groups which include hemiacetals, hemiketals, hemilactones, and hemiesters.

Examples of contrast agents include hydroxyl-containing X-ray contrast agents such as Iohexol; MRI contrast agents which contain a functional group useful for crosslinking to PVA, such as a chelating agent comprising hydroxyl groups in a bis-amide of DTPA (e.g. one formed by reaction of DTPA bis anhydride with two equivalents of 3-amino-1,2-propanediol (APD) or of a hydroxyl-protected form of 3-amino-1,2-propanediol (such as one in which the hydroxyl oxygens are linked by a prop-2,2-diyl group to form a five membered ring)) which is metallated with an MRI-active metal ion such as Gd+3; particulate MRI contrast agents such as iron oxide particles which comprise a coating or matrix of a polymer or polymer residue that contains one or more hydroxyl group (such as a magnetic iron oxide particle provided with a coating of oxidized starch, e.g. as described in WO97/25073); an ultrasound contrast agent comprising a phospholipid monoester and a free hydroxyl group; a nuclear imaging agent such as a chelating agent which is the N,N"bisamide reaction product of DTPA anhydride and APD and which is metallated with a radionuclide useful in diagnostic imaging such as 99mTc and ^{111}In. (The chelating agent could also be metallated by a radionuclide useful as a therapeutic agent such as 90Y.)

Interpenetrating networks of two or more polymers can be formed if the polymers are compatible and mix intimately with each other. Such combinations of polymers can be mixed together without solvent (i.e., neat) or in the presence of a solvent. Preferably, the solvent system used is compatible with each polymer and is not toxic relative to the toxicity of the polymers.

An example of a preferred solvent is water. Examples of contrast agents capable of forming interpenetrating networks with PVA include polymeric contrast agents, preferably linear polymers such as copolymers of a chelating agent such as DTPA and a soluble polymer such as a PEG, e.g. PEG diamine. Examples of such polymers have been disclosed in WO94/08624, WO95/26754 and WO94/09056. Particularly useful agents include DTPA-PEG diamine copolymers metallated by metal ions such as Gd+3 ions which function as MRI contrast agents.

When two polymer systems do not readily mix in the absence of a solvent, there is a tendency for the polymers to phase separate from each other. For example, a polymer may be dissolved in a solvent and applied to the surface of another polymer that is not readily soluble in that solvent. When the solvent is removed, the two polymers will be phase separated. The presence of polar groups in each polymer will produce adhesion between the two polymers. The adhesion may be enhanced by the presence of opposite charges; by the presence of polarizable and polarizing functional groups in the respective polymers; and by the presence of hydrogen bonding groups such as hydroxyl groups in the respective polymers. An example of two polymers that should demonstrate phase separation and mutual adhesion include PVA and a copolymer of DTPA and hexane diamine, the latter of which is bound to a metal ion such as Gd+3 and other metal ions referred to herein.

To form a crosslinked PVA particle loaded with a contrast agent as described above, a composition comprising PVA particles is first dispersed in boiling water to swell the particle. An aqueous solution or suspension of a contrast agent such as Iohexol or a suitable MRI contrast agent (i.e., a metal chelate or an iron oxide particle) listed herein or a mixture of more than one of these contrast agents is then added. The mixture is stirred well, optionally heated to boiling or

to a temperature between room temperature and the boiling point of the mixture, and optionally treated with a crosslinking agent such as an aqueous solution of formaldehyde. The reaction is allowed to proceed for a time sufficient to permit crosslinking between the PVA and the contrast agent, preferably from about 10 seconds to 24 hours. The solvent is then removed, for example, by spray drying the mixture or by lyophilization of the mixture, or by evaporation of the solvent from the mixture, or by a process comprising a combination of any of the methods to remove solvent.

Optionally, a crosslinking agent can be applied to combinations of polymers with PVA which form interpenetrating networks with PVA and which adhere to PVA.

Additionally, PVA is usually prepared by the radical polymerization of a vinyl ester such as vinyl acetate. In the polymerization process, usually the vinyl ester radicals polymerize in a head-to-tail fashion, but a small percentage of the vinyl esters react head to head. When the ester bonds are hydrolyzed to form PVA, most of the hydroxyl groups in the polymer are located on every other carbon. However, a small number of vicinal dihydroxy groups are present. These can be cleaved, for example, by periodate ion, to form transient radical species and thence aldehydes. The aldehydes can be used as sites of reaction with contrast agents, for example, through the formation of hemiacetals with hydroxyl-containing agents.

PVA may be loaded with Iohexol with and without additional formaldehyde. For example, PVA can be swollen with an iohexol solution, optionally after first adding water to the PVA, in a concentration of from 1% to 10,000% of Iohexol/PVA. The temperature of swelling can be from ambient temperature to boiling point of the solvent. The temperature may be held constant at a high temperature for an initial time, and then the mixture

may be cooled to a lower temperature and held at that temperature for another time. Concentrations of 0% or from 0.01% to about 10% of formaldehyde by weight of PVA may be used. Formaldehyde can be added initially prior to heating, after a time of heating, after cooling from a maximum temperature, or just prior to removal of solvent. Time of mixing and holding can be from about 1 minute to 24 hours. The solvent can be removed by distillation, by evaporation, for example, on a rotary evaporator at less than atmospheric pressure, by lyophilization, or by spray drying.

MRI contrast agents such as oxidized starch coated superparamagnetic iron oxide particles (see WO97/25073), PEG-DTPA Gd+3 copolymers and alkylene diamine-DTPA-Gd+3 copolymers may be used in place of or in addition to the soluble iodinated compound. Where alkylene diamine DTPA copolymers are used, it may be desirable to use ethanol as a cosolvent. Such cosolvents may be removed azeotropically prior to addition of formaldehyde.

The embolizing agent of the invention may be formulated for parenteral administration with conventional pharmaceutically acceptable carriers and excipients, e.g. aqueous carrier liquids such as water for injections, physiological saline and Ringer's solution, aqueous X-ray or mr contrast agent solutions, buffers, osmolality adjusting agents, emulsifiers, viscosity enhancers, etc. Thus viewed from a further aspect the invention provides an embolizing composition comprising a particulate embolizing agent according to the invention together with at least one pharmaceutically acceptable carrier or excipient, preferably in the form of a sterile, pyrogen-free suspension or dispersion.

In the compositions of the invention, the particulate agent is preferably present at a concentration of 0.5 to 100 mg particles/mL, preferably 1 to 50 mg/mL, especially 20 to 30 mg/mL.

The particulate embolizing agent in the compositions of the invention may advantageously contain a cytotoxic agent, e.g. cisplatin, carboplatin or paclitaxel or an angiogenesis inhibiting drug, so that the compositions may exert a double cytotoxic effect, part resulting from embolization of the target tissue and part resulting from localized release of the cytotoxic agent at the embolus site. Where the particulate agent contains a magnetically heatable or a gaseous contrast enhancing material, an oscillating magnetic field or high intensity ultrasound may be used to break down the particle and release any remaining cytotoxic agent after the embolus has been present for a period sufficient for a chemoembolization effect to have occurred.

Viewed from a yet further aspect the invention provides a method of chemoembolization therapy wherein a particulate embolizing agent is administered into the vasculature of a human or vascularized non-human (e.g. mammalian, avian or reptilian) body, the improvement comprising having as said agent an agent according to the invention.

Viewed from a further aspect the invention provides the use of an embolizing agent according to the invention for the manufacture of a medicament for use in chemoembolization therapy.

Thus the embolizing agent may be used in treating skin, head or neck tumors, tumors of the uterus or fallopian tubes, liver or kidney tumors, endometriosis, fibroids, etc.

In such treatments, a vasodilator (for example adenosine) may be administered beforehand, simultaneously or subsequently, in order to facilitate accurate placement of the embolus.

The embolizing composition is desirably administered by injection, or more preferably infusion, into the vasculature upstream of the target site, e.g.

in a dose of 1 to 200 mg, preferably 5 to 100 mg, particles administered over a period of 1 to 120 seconds, preferably 30 to 90 seconds.

Particularly preferably administration is by infusion of a relatively dilute suspension, e.g. 1 to 20 mg/mL, over a relatively prolonged period, e.g. 30 to 80 seconds.

The embolizing agents of the invention may also be used as contrast agents for diagnostic imaging modalities, e.g. following administration into an externally voiding body cavity such as the gastrointestinal tract, vagina, nose, bladder and lungs. In this aspect of the invention, the agents will be used at concentrations conventional for the administration route and the imaging modality used.

Documents referred to herein are hereby incorporated by reference.

The invention will now be described further with reference to the following non-limiting Examples.

EXAMPLE 1

Treatment of Polyvinyl Alcohol Particles with Iron(III)

0.1 g of Ultra Ivalon polyvinyl alcohol particles between 150 and 250 microns in effective diameter were placed into a glass scintillation vial with 10 ml of a 10% solution of $FeCl_3$. The suspension was then rotated for 24 hr to achieve equilibration of the PVA with the Fe(III) cation. At the end of this time, the particles were centrifuged and the supernatant decanted. The particles were then resuspended in deionized water followed by centrifugation and decantation. This cycle was repeated 3 times to remove the excess Fe(III) from solution. Upon completion of this process, the particles were deep yellow-red in colour clearly

demonstrating that Fe(III) had been partitioned into the particles themselves.

EXAMPLE 2

Treatment of PVA particles with Fe(III) followed by treatment with Iosulamide, an iodinated anion for precipitation

Ultra Ivalon particles treated as in Example 1 were exposed to a 20% solution of disodium iosulamide on a rotator for 24 hr. At the end of this time, the particles were centrifuged and the supernatant decanted to remove excess iosulamide from the PVA particles. The particles were resuspended in deionized water and then centrifuged and decanted again. This process was repeated 3 times to remove excess iosulamide.

The resulting particles were examined relative to untreated Ultra Ivalon particles by suspending both in saline and imaging both tubes by flat film X-ray at 40 kV/2 mA. The iosulamide treated particles exhibited some contrast even on this low sensitivity imaging modality while the untreated particles were translucent to the imaging x-rays.

EXAMPLE 3

Treatment of PVA particles with Fe(III) followed by treatment with Metrizoate, an iodinated anion for precipitation

Ultra Ivalon particles treated as Example 1 were exposed to a 50% solution of sodium metrizoate on a rotator for 24 hr. At the end of this time the particles were centrifuged and the supernatant decanted to remove excess metrizoate from the PVA particles. The particles

were resuspended in deionized water and then centrifuged and decanted again. This process was repeated 3 times to remove excess metrizoate.

The resulting particles were examined relative to untreated Ultra Ivalon particles by suspending both in saline and imaging both tubes by flat film x-ray at 40 kV/2 mA. The metrizoate treated particles exhibited some contrast even on this low sensitivity imaging modality while the untreated particles were translucent to the imaging x-rays.

EXAMPLE 4

Treatment of PVA particles with Gd(III)

0.1 g of Ultra Ivalon polyvinyl alcohol particles between 150 and 250 microns in effective diameter were placed into a glass scintillation vial with 10 ml of a 0.1 M solution of $GdCl_3$. The suspension was then rotated for 24 hr to achieve equilibration of the PVA with the Gd(III) cation. At the end of this time, the particles were centrifuged and the supernatant decanted. The particles were then resuspended in deionized water followed by centrifugation and decantation. This cycle was repeated 3 times to remove the excess Gd(III) from solution. Upon completion of this process, the particles were more white than the untreated particles to the observer.

EXAMPLE 5

Treatment of Gd soaked PVA particles with a solution of sodium oxalate

Ultra Ivalon particles treated as in Example 4 were exposed to a 0.1 M solution of sodium oxalate on a

rotator for 24 hr. At the end of this time, the particles were centrifuged and the supernatant decanted to remove excess oxalate from the PVA particles. The particles were resuspended in deionized water and then centrifuged and decanted again. This process was repeated 3 times to remove excess oxalate.

The resulting particles were examined relative to untreated Ultra Ivalon particles by suspending both in saline and imaging both tubes by flat film x-ray at 40 kV/2mA. The oxalate treated particles exhibited some contrast even on this low sensitivity imaging modality while the untreated particles were translucent to the imaging x-rays.

EXAMPLE 6

Treatment of Gd soaked PVA particles with a solution of iosulamide

Ultra Ivalon particles treated as Example 4 were exposed to a 20% solution of disodium iosulamide on a rotator for 24 hr. At the end of this time, the particles were centrifuged and the supernatant decanted to remove excess iosulamide from the PVA particles. The particles were resuspended in deionized water and then centrifuged and decanted again. This process was repeated 3 times to remove excess iosulamide.

The resulting particles were examined relative to untreated Ultra Ivalon particles by suspending both in saline and imaging both tubes by flat film x-ray at 40 kV/2mA. The iosulamide treated particles exhibited some contrast even on this low sensitivity imaging modality while the untreated particles were translucent to the imaging x-rays.

EXAMPLE 7

Treatment of Gd soaked PVA particles with a solution at elevated pH

Ultra Ivalon particles treated as in Example 4 were exposed to a solution of phosphate buffered saline (pH = 7.2) on a rotator for 24 hr. At the end of this time, the particles were centrifuged and the supernatant decanted to remove excess buffer from the PVA particles. The particles were resuspended in deionized water and then centrifuged and decanted again. This process was repeated 3 times to remove excess ions.

The resulting particles were examined relative to untreated Ultra Ivalon particles by suspending both in saline and imaging both tubes by flat film x-ray at 40 kV/2mA. The PBS treated particles exhibited some contrast even on this low sensitivity imaging modality while the untreated particles were translucent to the imaging x-rays.

EXAMPLE 8

Treatment of PVA particles with molecular iodine

0.1 g of Ultra Ivalon polyvinyl alcohol particles between 150 and 250 microns in effective diameter were placed into a glass scintillation vial with 10 ml of a 5 % solution of iodine. The suspension was then rotated for 24 hr to achieve equilibration of the PVA with the iodine. At the end of this time, the particles were centrifuged and the supernatant decanted. The particles were then resuspended in deionised water followed by centrifugation and decantation. This cycle was repeated 3 times to remove the excess iodine from solution. Upon completion of this process, the particles were deep

blue/black in colour clearly demonstrating that iodine had been partitioned into the particles themselves.

Further, these particles were examined by conventional x-ray imaging at 40 kV/2mA and found to afford x-ray contrast not present in untreated Ultra Ivalon particles.

EXAMPLE 9

Treatment of iodine soaked PVA particles with a solution of silver nitrate

Ultra Ivalon particles treated as in Example 8 were exposed to a solution of silver nitrate on a rotator for 24 hr. Immediately upon exposure to the silver solution, the particles became white indicating the rapid reaction between the silver and the iodine in the particles. At the end of 24 hr, the particles were centrifuged and the supernatant decanted to remove excess silver nitrate from the PVA particles. The particles were resuspended in deionized water and then centrifuged and decanted again. This process was repeated 3 times to remove excess silver ions.

The resulting particles were examined relative to untreated Ultra Ivalon particles by suspending both in saline and imaging both tubes by flat film x-ray at 40 kV/2mA. The silver treated particles exhibited some contrast even on this low sensitivity imaging modality while the untreated particles were translucent to the imaging x-rays. While iodine treated PVA particles afford x-ray contrast on their own, the addition of silver ion resulted in precipitation of silver iodide on and within the particles thus maintaining or enhancing the x-ray contrast effect and lowering the solubility of the contrast agent (i.e., silver iodide vs molecular

iodine) for improved stability within the particles after embolus formation.

EXAMPLE 10

CT imaging of PVA sponges containing precipitated heavy metal salts

Sponges of PVA were prepared as detailed in Examples 1-7, sealed in clear plastic pouches filled with saline and imaged by CT using a Toshiba CT scanner at 140 kV with intensities reported in Hounsfield Units (HU). The Table 1 below indicates which materials afforded CT contrast and to what level.

Table 1. CT Enhancement of Various Metal Salt/PVA Combinations

Sample	CT Enhancement (HU)
FeIII (Iosulamide)	458
FeIII (Ioxaglate)	373
FeIII (Diatrizoate)	89
FeIII (Iodipamide)	60
GdIII (Iosulamide)	126
GdIII (Iodipamide)	143

A CT image of seven PVA sponges scanned in air at 150 kV/150 mA is shown in Figure 1. Sponges 1 to 7 were loaded as follows:

(1) $FeCl_3$, (2) FeIII + Iosulamide, (3) FeIII + Metrizoate, (4) FeIII + Hexabrix, (5) FeIII + Isovue, (6) FeIII + Diatrizoate, (7) FeIII + Iodipamide.

EXAMPLE 11

Treatment of polyvinylalcohol particles with Ag(I) ions

0.55g of Ultra Ivalon polyvinyl alcohol particles between 150 and 250 microns in effective diameter were placed into a glass scintillation vial with 10 ml of a 1M solution of $AgNO_3$. The suspension was then rotated for 24 hours to achieve equilibration of the PVA with the Ag(I) cation. At the end of this time, the particles were filtered to remove them from the silver solution and rinsed briefly with ultrapure water. The particles were then resuspended in a 2M solution of potassium iodide and rotated for 24 hours to reach equilibrium. The particles were then filtered and rinsed with water. They were then recovered into a glass scintillation vial with water and lyophilized into a free flowing powder. Assessment by flat film x-ray at 40 kv/2 ma showed absorption of x-rays by the treated particles indicating the formation of the insoluble silver iodide salt within the PVA particles.

EXAMPLE 12

Precipitation of insoluble, iodinated x-ray contrast agent within PVA particles for CT opaque embolic agents

0.55 gm of PVA particles with an average diameter of 150 to 250 microns were added to 10 ml of a 10% (wt/vol%) solution of a water-insoluble tri-iodinated sulphonamide which had been solubilized by the addition of sufficient sodium hydroxide to result in deprotonation of the sulfonamido nitrogen atom. After 24 hours to equilibrate, the particles were filtered and added to a solution of acetic acid (1N) whereupon the particles changed to an opaque yellow appearance signifying the precipitation of the insoluble iodinated contrast agent

within the particles due to the drop in pH. These particles were assessed by x-ray fluorescence and flat film imaging and demonstrated enhanced x-ray opacity as a result of the incorporation of the insoluble iodinated contrast agent.

The sulphonamide used in this Example is the title compound of Example 21 of WO96/23524.

EXAMPLE 13

Use of contrast enhanced PVA particles to cause uterine artery embolization for uterine fibroids

PVA particles prepared analogously to Example 11 are used in the embolization of uterine fibroids which are responsible for a number of symptoms including vaginal bleeding, abdominal pain, and swelling. The particles are between 500 and 700 microns in diameter by light scattering (Fraunhoffer scattering, Horiba 910A). A dose of approximately 500 mg is administered bilaterally via a 4 French C1 glidecatheter (Meditech Corp., Watertown, MA) or a 5 French Levin-1 catheter (Cook, Inc., Bloomington, IN) through the anterior division of the contralateral internal iliac artery with subselective catheterization into the uterine artery. Embolus placement is monitored both by the use of soluble contrast agent in an angiographic mode (i.e., 50 to 100 ml of Omnipaque 300 - an iohexol containing contrast medium) and by imaging of the embolus itself due to the contrast provided by the precipitated silver iodide. Complete embolization of the uterine fibroid is determined in this way.

Followup imaging is carried out 2 weeks post embolization by imaging with both conventional X-ray and CT scans of the abdomen. Weak contrast may be seen in

the embolus itself by flat film X-ray while excellent CT contrast may be observed for the embolus. Embolus location may be confirmed by the use of angiographic contrast media and conventional imaging.

EXAMPLE 14

Use of contrast enhanced PVA particles to embolize the kidney

PVA particles prepared analogously to Example 12 were used in the embolization of the kidney. The particles were between 500 and 700 microns in diameter by light scattering (Fraunhoffer scattering, Horiba 910A). A dose of approximately 250 mg was administered bilaterally via a 4 French C1 glidecatheter (Meditech Corp., Watertown, MA) or a 5 French Levin-1 catheter (Cook, Inc., Bloomington, IN) through the renal artery. Embolus placement was monitored both by the use of soluble contrast agent in an angiographic mode (i.e., 50 to 100 ml of Omnipaque 300) and by imaging of the embolus itself due to the contrast provided by the precipitated iodinated contrast agent. Complete embolization of the kidney was determined in this way.

Imaging at 2 weeks post embolization may confirm the presence of the embolus by both conventional imaging and CT scanning of the abdomen.

EXAMPLE 15

Use of contrast enhanced PVA particles to embolize an arteriovenous malformation (AVM)

PVA particles prepared analogously to Example 7 are used in the embolization of the AVM. The particles are between 500 and 700 microns in diameter by light

scattering (Fraunhoffer scattering, Horiba 910A). A dose of approximately 250 mg is administered bilaterally via a 4 French C1 glidecatheter (Meditech Corp., Watertown, MA) or a 5 French Levin-1 catheter (Cook, Inc., Bloomington, IN) through the feeding artery. Embolus placement is monitored via MRI both by the use of soluble contrast agent in an angiographic mode (i.e., 5 to 10 ml of Omniscan - a gadodiamide containing contrast medium) and by imaging of the embolus itself due to the contrast provided by the precipitated Gd. Complete embolization of the AVM is determined in this way. Both agents may provide T1 weighted images of the location of the embolus.

Claims

1. An embolizing composition comprising a particulate biotolerable organic polymer having immobilized therein or on the surface thereof a contrast enhancing material.

2. A composition as claimed in claim 1 wherein said polymer is a polyvinyl alcohol.

3. A composition as claimed in either claim 1 or claim 2 wherein said material is an iodinated organic compound.

4. A composition as claimed in claim 1 wherein said material is a paramagnetic or superparamagnetic material.

5. An embolizing agent comprising polyvinyl alcohol particles containing an immobilized contrast enhancing material selected from water-insoluble compounds, and or complexes of paramagnetic metals, superparamagnetic metal oxide particles, water-insoluble compounds, salts and complexes of heavy metals, lipophilic gases and gas mixtures, entrapped gases and gas mixtures, water-soluble iodinated organic compounds, water-insoluble iodinated organic compounds, and water-insoluble compounds, salts and complexes of metal radionuclides.

6. A process for the production of an embolizing agent as claimed in claim 5, said process comprising treating a porous particulate biotolerable organic polymer according to at least one of the following steps: precipitation of a water insoluble material within the pores of the polymer particle from a gaseous or dissolved precursor; immersion of porous polymer particles in contrast agent solution followed by cross-linking of the polymer, immersion of polymer particles

in contrast agent solution followed by treatment to promote bond creation; immersion in a liquified lipophilic gas or gas mixture; or reaction of the polymer surface with a reagent serving to couple to the surface a contrast enhancing material; and encapsulation of a physiologically tolerable gas or gas mixture within a biotolerable organic polymer.

7. An embolizing composition as claimed in any of claims 1 to 4 comprising a particulate embolizing agent according to claim 5 together with at least one pharmaceutically acceptable carrier or excipient.

8. In a method of chemoembolization therapy wherein a particulate embolizing agent is administered into the vasculature of a human or vascularized non-human body, the improvement comprising using as said agent an agent according to claim 5.

9. The use of an embolizing agent according to claim 5 for the manufacture of a medicament for use in chemoembolization therapy.

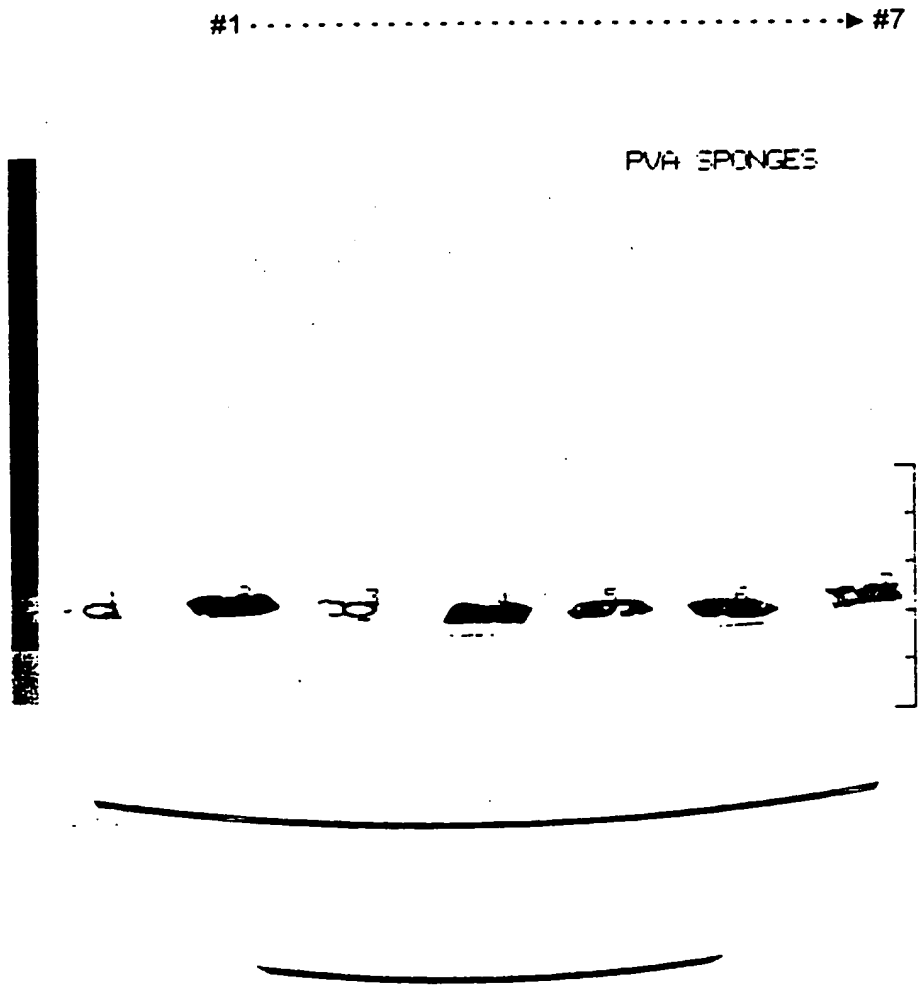

FIG. 1

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 98/02621

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K49/00 A61K49/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MAVLIGIT ET AL : "Gastrointestinal leiomyosarcoma metastatic to the liver" CANCER, vol. 75, 1995, pages 2083-88, XP002085328 * abstract; p.2084, 2nd col., last sentence bridging p.2084 and p.2085 *	1-9
X	WO 89 11874 A (BRAYBROOK JULIAN HUGH ;HALL LAURENCE DAVID (GB)) 14 December 1989 * claims 1-19; p.9, 1st full par.; last par. bridging p.9-10 *	1,4

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 November 1998	08/12/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Uiber, P

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 98/02621

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MARTINELLI ET AL: "Utility of emobolization or chemoemobolization as second-line treatment in poatients with advanced or recurrent colorectal carcinoma" CANCER, vol. 74, 1994, pages 1706-12, XP002085329 * Abstract; p.1710, right hand col., last par.; p.1711, last par. *	1-9
X	TOUHO ET AL: "Intravascular treatment of spinal arteriovenous malformations using microcatheter with special reference to serial xylocaine tests and intravascular pressure monitoring" SURG. NEUROL., vol. 42, 1994, pages 148-56, XP002085330 * Abstract; p.149, 1st col., last par. *	1-9
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1

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Information on patent family members

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PCT/GB 98/02621

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